Infantile Spasm

Response of "Salaam Seizures" to Hydrocortisone

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• **Two groups of children with salaam seizures were studied—16 treated with routine anticonvulsants (control group) and 20 who had hydrocortisone added to their routine medication (Cortef-plus group). Results in the two groups were similar.**

INFANTILE SPASMS, hypsarrhythmia, or "salaam seizures" were described in 1841 by West, who emphasized an associated arrest in intellectual development of the infant. Lennox and Davis[9] in 1950 correlated massive myoclonic spasms in infants with electroencephalograph tracings which were characterized by one to two high amplitude waves per second, with spiking of multifocal origin. Gibbs and Gibbs[3] introduced the now familiar term *hypsarrhythmia* to describe the chaotic electroencephalographic pattern seen at one time or another in approximately 80 per cent of patients with this syndrome. Treatment with the usual anticonvulsant drugs is usually of no avail. However, widespread interest has been aroused since the report of Sorel and Dusaucy-Bauloye[15] in 1958 on the beneficial and dramatic effects of steroids in this condition.

It has been recognized that infants with this syndrome can be divided into two main categories: (1) the symptomatic group — those in whom there is a history of previous insult to the nervous system which usually results in retardation in development before the onset of seizures; (2) the cryptogenic group — those in whom no history of insult is obtained and in whom development is entirely normal before the seizures occur. On this basis, lack of success with treatment is of less concern in the average member of the symptomatic group, especially where previous damage to the central nervous system has left the child permanently retarded.

Our report presents a comparison of results in a group of children treated with routine anticonvulsant drugs and an equivalent group treated with oral hydrocortisone in addition to the anticonvulsants.

Thirty-six patients between the ages of three months and five years were selected for the study (Table 1). Sixteen of them who had been diagnosed and observed before 1958 served as the control group. The remaining 20, who were observed after 1958, received oral hydrocortisone (Cortef®) 30 mg per day in divided doses for periods up to 18 months. They also received the same drugs that were given to the control group. The steroid was given by mouth because of the ease of administration at home.

The groups were comparable as to sex ratio, age at the first visit, mean age at onset of seizures, and mean duration of seizures at the time of first visit. Table 2 indicates presumptive factors in the pathogenesis of the seizures in both groups. In ten of the 16 control patients and 11 of the 20 steroid-treated patients such factors were present.

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TABLE 1 — Nature of Patients with Hypsarrhythmia Treated by Two Different Methods

	Control Group	Cortef-Plus* Group
Total number of patients	16	20
Male	9	10
Female	7	10
Age at initial visit:		
Youngest	3 mo	2 mo
Oldest	5 yr.	4½ yr
Mean age at onset of seizures:	7 mo	9½ mo
Duration of seizures at initial visit:		
Minimal	1 mo	2 mo
Maximal	3¾ yr	2¼ yr
Mean	9 mo	9 mo

*Received Cortef in addition to the therapy given to controls.

TABLE 2 — Presumptive Factors in Pathogenesis of Hypsarrhythmia in Two Groups of Patients

	Control Group (16)	Cortef-Plus Group (20)
Positive family history of seizures	2	3
Prenatal and perinatal factors (perinatal trauma, phenylketonuria, etc.)	3	4
Postnatal factors		
Immunization	1	3
Infection (croup, measles encephalitis, chicken pox, toxoplasmosis)	3	1
Cerebral lipidosis	1	-
Unknown	6	9

TABLE 3 — Results of Treatment With and Without Steroids

	Control Group (16)	Cortef-Plus Group (20)
Good effect on seizures and development (see Table 4)	2	7
Good effect on seizures but not on development (see Table 5)	2	6
No effect on seizures or development	10	7
Insufficient follow-up	2	-

RESULTS

Results of treatment are summarized in Table 3 according to whether drug therapy affected the frequency of seizures and whether there was an associated improvement in overall development with this reduction in frequency.

It will be noted that treatment in seven of the 20 patients in the group receiving Cortef in addition to the other treatment (Cortef-plus group, Table 4) and two of the 16 patients in the control group had a beneficial effect on the seizures as well as on development. Similarly, six patients (Table 5) in the Cortef-treated and two in the control group had a reduction in frequency of seizures without a corresponding improvement in development, while seven of the steroid-treated patients (Table 6) and ten in the control group were refractory to treatment.

In order to learn more about the reasons for an apparent improvement of 13 of the steroid-treated patients and four of the control group, a more detailed analysis was undertaken. Of the seven infants (Table 4) in the steroid-treated group who showed a global response to hydrocortisone treatment, the first six were considered to have had normal development up to the onset of seizures. Four of the six had no obvious factors associated with the syndrome and fitted into the cryptogenic classification, while three had onset of seizures following administration of inactivated poliomyelitis vaccine. In this group, the mean age of onset of seizures was five months, while the mean duration of seizures before steroid medication was six months.

On analysis, this improvement is somewhat illusory — three of the seven infants were considered to be normal between one and two years following institution of treatment; the other four infants, in whom seizures had either ceased or were drastically reduced and in whom motor development was considered to be good, all showed a delay in speech.

Of the six infants in whom seizures but not development were improved with hydrocortisone medication (Table 5), five were considered to be retarded before the onset of seizures. Of these, two were judged to have suffered central nervous system insult during the perinatal period and in the other three no obvious factors were elicited in the history.

TABLE 4 — Data on Seven Patients in Steroid-Treated Group Who Had Beneficial Effect on Seizures and on Development

Patient	Sex	Age in Months	Age of Onset of Seizures (Months)	Duration of Seizures (Months)	Age Cortef Started (Months)	Response		Family History of Seizures	Perinatal Trauma	Associated Factors	Present Status
						Development	Seizure Control				
1	M	9	5	4	5	+	+++	—	—	5 days after polio innoc.	Age 21 mos. No attacks for 9 mos. Motor development normal. No speech.
2	F	7	5	2	7	+++	+++	—	—	7 days after polio innoc.	Age 24 months. Normal
3	M	11	6	5	11	+++	+++	—	—	—	Age 18 months. Normal
4	F	15	4	11	15	** Normal	+++	Mat. aunt breath holding spells	—	—	Age 25 months. Normal
5	M	9	3	6	5	++	+++	—	—	Vomiting in 1st 2 mos of life	Age 12 months. Attacks 4/day Development continues.
6	M	14	6	8	14	+++	+++	—	—	—	Age 30 mos. No attacks. Physical and emotional development good, but delayed speech.
7	M	11	6	5	11	+++	+++	Mat. uncle died age 29 Mat. cousin died age 12	1 mo. premature & jaundiced for 6 days	14 days after polio innoc.	Age 30 mos. No attacks. Physical and emotional development good, but delayed speech.
Mean (months)		11	5	6	10	—	—	—	—	—	—

+ = Slight ++ = Moderate +++ = Marked ** = Ref. Table 7

Presumably their basic defect was of prenatal origin. On this basis, at least five and possibly six infants fall into the symptomatic category. It is, therefore, not surprising that steroid medication did not modify their development although it illustrates that seizures may respond to hydrocortisone regardless of whether the infant falls into the symptomatic or cryptogenic category. The response was evident, despite a lapse of 12 months, compared with six months in the control group, before the commencement of hydrocortisone therapy.

Of the seven infants who were refractory to hydrocortisone medication (Table 6) two had onset of seizures within three days of birth and, in the absence of evidence to the contrary, it is presumed that prenatal factors were causative. Unfortunately, no permission was obtained for autopsy in the one infant who died at four months. One infant was born by cesarean section at the eighth month with symptoms of hypoxia at delivery. All of the six living infants were severely retarded: two had been put into institutions by the second year, and two were unimproved at 36 and 54 months despite continuous hydrocortisone therapy for 18 and 16 months, respectively.

The outstanding difference between this group (Table 6) and the other two (Tables 4 and 5) appeared to be the mean age of onset of the seizures — two months — as compared with five months (Table 4) and seven months (Table 5).

Also analyzed were the factors which concerned the three patients in the cryptogenic category (two in the control group and one in the steroid-treated group) who were normal when first seen and

TABLE 5 — Data on Six Steroid-Treated Patients Who Had Reduction in Seizures But No Improvement in Development

Patient	Sex	Age in Months	Age of Onset of Seizures (Months)	Duration of Seizures (Months)	Age Cortef Started (Months)	Response		Family History of Seizures	Perinatal Trauma	Associated Factors	Present Status
						Development	Seizure Control				
8	F	7	3	4	7	0	++	—	Forceps Hypoxia	—	Institution — Age 10 mos.
9	M	17	6	12	17	0	++	Mother in childhood	—	—	Age 36 mos. Motor development normal. No speech.
10	M	51	24	27	51	0	++	—	Premature	—	Age 57 mos. Occasional attack. Severely retarded.
11	M	7	1	6	7	0	+++	—	—	—	Age 19 mos. No attacks — but institution
12	F	16	2	14	16	0	+++	—	—	—	Age 18 mos. No attacks. Severely retarded.
13	F	11	4	7	11	+	+++	—	—	—	Age 24 mos. No attacks. Development slight.
Mean (Months)		18	7	12	18	—	—	—	—	—	—

0 = Minimal + = Slight ++ = Moderate +++ = Marked

TABLE 6 — Data on Seven Steroid-Treated Patients Who Were Refractory to Treatment

Patient	Sex	Age in Months	Age of Onset of Seizures (Months)	Duration of Seizures (Months)	Age Cortef Started (Months)	Response		Family History of Seizures	Perinatal Trauma etc.	Associated Factors	Present Status
						Development	Seizure Control				
14	M	7	3 days	7	7	0	0	—	—	—	Age 8 months. No improvement
15	F	31	3	28	31	0	0	—	—	Toxoplasmosis ?	Not known
16	M	7	4	3	7	0	0	—	—	—	Age 27 mos. Institution. No improvement.
17	F	18	1	17	18	0	0	—	—	—	Age 36 mos. No improvement. Cortef = 18 mos.
18	F	24	6	18	24	0	0	—	—	—	Age 54 mos. No improvement. Cortef = 6 mos.
19	F	2	3 days	2	2	0	0	—	—	—	Died 4 mos. No autopsy.
20	F	5	2	3	5	0	0	—	1 mo. prem. Caesarian Hypoxia +	—	Age 24 mos. Institution. Cortef = many months.
Mean (Months)		13	2	11	13	—	—	—	—	—	

0 = Minimal

TABLE 7 — Patients in Cryptogenic Category (two in control group, one in Cortef-treated group) Who Were Normal When First Observed and Responded Satisfactorily to Treatment

Patient	Age in Months	Age of Onset of Seizures (Months)	Duration of Seizures (Months)	Frequency of Seizures Per Day	Physical Exam.	Medication	Effect of Medication	Present Status
Case A (Control)	6	5	1	+++	Normal	Phenobarbital Phenurone	No attacks after 2 weeks	Age 7 yrs — Normal (School 3rd grade)
Case B (Control)	7	6	1	+++	Normal	Phenobarbital Ketogenic Diet	No attacks after 2 days	Age 3 years Normal
Case 4 (Table 4)	15	4	11	+++ for 18 mos. then- +	Normal	Gemonil Cortef	Stopped attacks	Age 2 years Normal

+ = Slight +++ = Marked

who responded satisfactorily to the treatment they received.

Both patients in the control group (Table 7) were diagnosed one month after the onset of seizures and showed dramatic response within a few days after receiving the usual anticonvulsive agents. Their seizures stopped and both children were considered to be normal at seven years and three years. The reason for the prompt response is not clear.

The last patient in Table 7 is of particular interest for, despite seizures for 11 months before the first visit, she was otherwise considered to be entirely normal. This would seem to refute the suggestion that seizures *per se* cause retardation or, indeed, that seizures over a prolonged period inevitably result in permanent damage to the nervous system. In this patient, after eight months of severe seizures there was a spontaneous reduction in severity without any specific adjustment in the routine anticonvulsant therapy which was being given at the time. This illustrates a fact which necessarily complicates the assessment of long term therapy — that is, that the syndrome is self-limiting regardless of the pathogenesis. Spasms start in most of these infants within the first six months of life and continue with varying severity until sometime between the second and fourth year. At this time, whether medication has been given or not, the salaam seizures begin to decrease. More familiar seizure patterns — that is, those of the major or minor variety — may at any time complicate the salaam syndrome and continue despite the fading of the salaam seizure. However, few infants continue with salaam seizures beyond five years.

DISCUSSION

Initial reports on the treatment of the syndrome with steroids were all encouraging. Sorel[15] treated 11 children with systemic ACTH and achieved good results in six and felt that when treatment was started within the first month of symptoms, intellectual arrest could be spared.

Stamps et al[16] in the following year reviewed the results of 60 patients with infantile spasms with short term treatment with ACTH. Their criteria for a good response, with which we are in full agreement, consisted of attempts to prevent further retardation, control of the seizures, and normalization of the electroencephalogram. They reported an overall response of 30 per cent to treatment, an elimination of seizures in 18, and a decrease in 13. Motor performance and alertness were considered to be normal in six and improved in 18.

Low et al[10] reporting on ten children drew a parallel between them and children with phenylketonuria (one patient in our control group showed this metabolic error) though he felt that some of these children might have another underlying metabolic defect. Three children were given diets deficient in aromatic amino acids for three to five months, without clinical or electroencephalographic improvement (one child had a brief response on a tryptophan-deficient regimen). Low was the first to use cortisone, as well as ACTH, in treatment of children with this diagnosis. His study indicated that results were the same regardless of the type or route of medication.

Subsequent reports by Trojaborg,[17] Kiorboe and Dangaard,[1] and Dumeruth[5] all stressed the fact that while steroids could markedly diminish seizures, the response in terms of cessation of mental retardation was extremely disappointing (with which we would also agree). If one accepts the arrest of intellectual deterioration as the important criteria for improvement, then consideration must be given to the two distinct groups — the symptomatic and the cryptogenic. Unfortunately, few previous studies have given this factor sufficient consideration, with the result that it is extremely difficult to analyze the conclusions of any author.

A notable exception to this are the reports by Jeavons[8] and Bower[3] in 1961. Thirty control patients followed for periods of time varying from two to six years without steroid therapy were compared with 20 patients who received steroid therapy. The value of their study lies in the detailed and objective assessments made of both groups in regard to (a)

the natural history of untreated infantile spasms, (b) objective recording of intellectual improvement, and (c) detailed electroencephalograph studies. In the control group there was a steady reduction in the number of patients who still had spasms at three years; over 50 per cent were entirely free of them. They stressed, however, that mental improvement was much rarer: only two of the 30 patients were mentally normal. There was slight difference between the symptomatic and cryptogenic groups with regard to the rate of spasm disappearance and improvement in electroencephalogram. Mental retardation was less severe in the cryptogenic group and was more apt to show a slight but definite general improvement later, whereas none occurred in the symptomatic group. In the steroid-treated group, corticotrophin or prednisolone was used for at least four weeks. Spasms ceased during the steroid treatment of 18, but recurred in 13 following cessation of therapy. No immediate mental improvement was noted in the steroid group — only two of the 23 patients achieved a developmental quotient of 80 or more. They concluded that "on the whole, in comparing the two groups, steroids have a long-term beneficial effect on the spasms, whereas their effect on mentality is doubtful." Our results are in accord with this: 13 of our 20 Cortef-treated patients had a moderate to marked response in seizure activity while only three of the 20 showed a normal mentality.

The overall response to therapy of any type must, of necessity, be dependent upon the individual pathogenesis. Unfortunately few pathologic studies have been reported. In our own series of patients, three of the control group are known to have died. Unfortunately no necropsy was performed on two; the third, at autopsy revealed pathologic changes of the early juvenile (Bielschowsky-Jansky) variant of cerebromacular degeneration. A fourth child in the control group had phenylketonuria.

Poser and Low[12] in 1960 reported the pathologic findings in three cases of infantile spasms which showed the same basic pathologic process, characterized by a chronic edema of varying intensity which resulted in a spongy degeneration. In the first case the grey matter was primarily involved, in the second the white matter with sparing of the grey, while the third showed involvement both of grey and white matter. Demyelinization was not a prominent feature in any of these cases. The findings were likened to some of the leukodystrophies, in particular those described by van Bogaert and Bertrand[18] as a "familial idiocy with spongy degeneration of the neuraxis." However, they pointed out that this latter condition, in addition to the status spongiosis of the grey and white matter, has extensive demyelinization which was absent in the three cases. Trojaborg[17] found severe cortical and subcortical destruction with an intense glial reaction. The etiology underlying the pathological picture of "infantile encephalomalacia" is mostly inferential and has been discussed at length by Wolf and Cowan.[20]

In contrast to the cryptogenic group, autopsy findings in the symptomatic group are related to the causative factor; e.g. reports by Paludin,[11] and Sinton[14] confirm the changes associated with perinatal trauma.

Mechanism of action of steroids

Despite the many reports on the use of steroids in this syndrome, the mechanism by which they achieve their effect is far from clear. Gastaut[6] and Roger[13], among others, have shown that in man ACTH and hydrocortisone have convulsant properties which are reflected in animals by their ability to lower the convulsive threshold. Yet, in infants with salaam seizures, and in children with minor seizures associated with three per second spike-wave discharges, their effect is reversed, so that both the clinical seizure and the associated abnormal electroencephalogram improve. Bower[2] pointed out that the mechanism by which this effect is achieved must be more fundamental than the action of routine anticonvulsants, where the electroencephalographic abnormality usually persists unchanged.

Hypoglycemia or imbalance of electrolytes has not been demonstrated in this syndrome.

It is of interest that the beneficial effects of steroids on salaam seizures and petit mal diminish at puberty and this would suggest that in the earlier age group steroids influence the maturation of enzyme systems.

Cochrane[4] found evidence of pyridoxine deficiency in five patients with salaam seizures and reported improvement after large doses of pyridoxine. Pyridoxine in the form of pyridoxal phosphate is important when it is realized that it is concerned in the formation of 5-hydroxytryptamine (Serotonin), an inhibitor of synaptive transmission, and gamma-amino-butyric acid (GABA), an anticonvulsant. For this reason, it is evident why tryptophan deficiency can lead to seizures. Despite this, Bower[2] failed to show improvement in three of his patients with systemic pyridoxine therapy.

It is also unsatisfactory to postulate that steroids achieve an effect through their anti-inflammatory properties. If this were so, no effect would be expected in the symptomatic group, where the basic insult has occurred some months before the onset of seizures. For lack of information, we must therefore rely upon empiric treatment.

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